REVIEW

Uremic Toxins, CKD, and Cognitive Dysfunction

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Abstract

Cognitive impairment involves alterations to one's cognitive status that affects everyday life. Individuals with CKD, and particularly kidney failure, experience higher rates of cognitive impairment (20%–70%) compared with the general population. The highest prevalence is described in kidney failure such that dialysis-dependent patients have twice the prevalence of age-matched controls. In the past 5 years, the number of investigations examining the "kidney-brain axis," mechanisms of CKD-related cognitive impairment, and potential therapeutics have exponentially increased. This review article summarizes recent literature on direct and indirect effects of CKD-associated cognitive impairment with emphasis on uremic toxins; brain injury mechanisms; overlap between CKD-associated cognitive impairment, Alzheimer's disease, and other neurodegenerative diseases. Reviewed therapeutic interventions include AST-120 (indoxyl sulfate absorbent), CH-223191 (aryl hydrocarbon receptor antagonist), triarylmethane-34 (Kca3.1-specific inhibitor), anakinra (IL-1R inhibitor), marimastat, exercise, supplements, and kidney transplantation. Special focus is placed on translational studies examining uremic toxin–associated pathogenic processes, including brain oxidative stress, neuroinflammation, and blood-brain barrier dysfunction through *in vitro* and *in vivo* models of CKD-associated brain injury. Finally, future research directions are suggested, including targeting of cellular senescence abundance with senotherapeutics and capitalizing on anti-inflammatory effects of regenerative, cell-based therapeutics (*e.g.*, mesenchymal stem cells and extracellular vesicles), and use of aged murine models. Collectively, CKD-associated cognitive impairment represents a prevalent condition for which remaining knowledge gaps exist, and scientific advancements are needed to preserve cognitive function and improve the lives of individuals with CKD.

JASN 36: 1208–1226, 2025. doi: https://doi.org/10.1681/ASN.0000000675

Introduction

CKD affects more than one in seven adults in the United States and more than 700 million individuals worldwide.[1,2] With progressive kidney function loss, metabolic waste products in the form of uremic toxins accumulate in the heart, vasculature, bone, bone marrow, and brain.[3] Change in brain function is among the many CKD sequela affecting patients' physical function and quality of life. Cognitive impairment, mild cognitive impairment, and dementia represent different degrees of severity to changes in cognition. Cognitive impairment can be measured through the clinical dementia rating, a widely used tool that assesses decline in cognition and function.[4,5] In mild cognitive impairment, while individuals may show impairments, daily life is mainly unaffected.[6] Typically, when social and/or occupational functioning is affected by the severity in decline in cognition, dementia is diagnosed.[7] What differentiates mild cognitive impairment and dementia is the loss of independence.[8] Although symptomatic Alzheimer's disease is the leading cause of dementia, Alzheimer's disease is defined by the presence of amyloid-β plaques and tau-tangles.[8] Mild cognitive impairment can be the earliest cognitive sign of Alzheimer's disease.[6] Mild cognitive impairment may also be attributed to other diseases, such as neurologic, neurodegenerative, or systemic, including CKD.[6]

Cognitive impairment can be highly prevalent in CKD, affecting up to 70%, increasing with kidney function loss, and highest among individuals with kidney failure.[9] In fact, the prevalence of cognitive impairment in dialysis-dependent patients is twice that of age-matched controls.[10] Since 2019, an exponential increase in the number of investigations examining the kidney-brain axis relationship, mechanisms of CKD-associated cognitive impairment, and potential treatments has occurred. However, knowledge gaps remain in the understanding of CKD and cognitive impairment, including the relationship between CKD and other common causes of cognitive impairment, specifically Alzheimer's disease and Alzheimer's disease–related dementias.

This article reviews recent literature on CKD-associated cognitive impairment with emphasis on uremic toxins, prevalence and shared risk factors, direct and indirect effects of CKD on Alzheimer's disease/Alzheimer's disease–related dementias, and promising therapeutics. Furthermore, a detailed review of translational studies examining uremic toxin–associated pathogenic processes, including brain oxidative stress, neuroinflammation,

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Published Online Ahead of Print: February 26, 2025

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and blood–brain barrier dysfunction through *in vitro* and *in vivo* models of CKD-associated brain cellular dysfunction as well as studied therapeutic interventions is summarized. Finally, additional pathogenic targets including cellular senescence are highlighted, and the role of regenerative, cell-based therapeutics are introduced.

Cognitive Impairment: Prevalence and Shared Risk Factors in CKD, Dialysis, and Kidney Transplantation

CKD is one of the strongest risk factors for cognitive impairment and dementia.[11] Cognitive impairment can be as high as 62% in patients with predialysis CKD compared with 26% in matched controls, suggesting that those with CKD are nearly three times more likely to experience cognitive impairment than the general population.[11] As shown in Figure 1, multiple risk factors have been identified that make those living with CKD more susceptible to cognitive impairment, dementia, and neurodegenerative diseases such as Alzheimer's disease. These traditional and nontraditional factors include age, sex, race, education level, hypertension, stroke, vascular disease, cerebrovascular disease, diabetes mellitus, exercise and activity, sleep disorders, and obesity. Intradialytic hypotension events during hemodialysis procedures may increase dementia risk, particularly in the elderly.[12] Increasingly, race-based differences for CKD and Alzheimer's disease/Alzheimer's disease–related dementias are thought to be attributed to systemic and structural racism.[13,14] Race-based differences may also be linked to social determinants of health, which have been associated with a higher risk of dementia diagnosis among people who live in or receive dialysis in high-segregation neighborhoods.[15] The current review will focus on mechanisms contributing to kidney-brain axis dysfunction.

Cognitive Impairment and CKD

A summary of clinical studies evaluating the relationship between cognitive impairment and CKD is presented

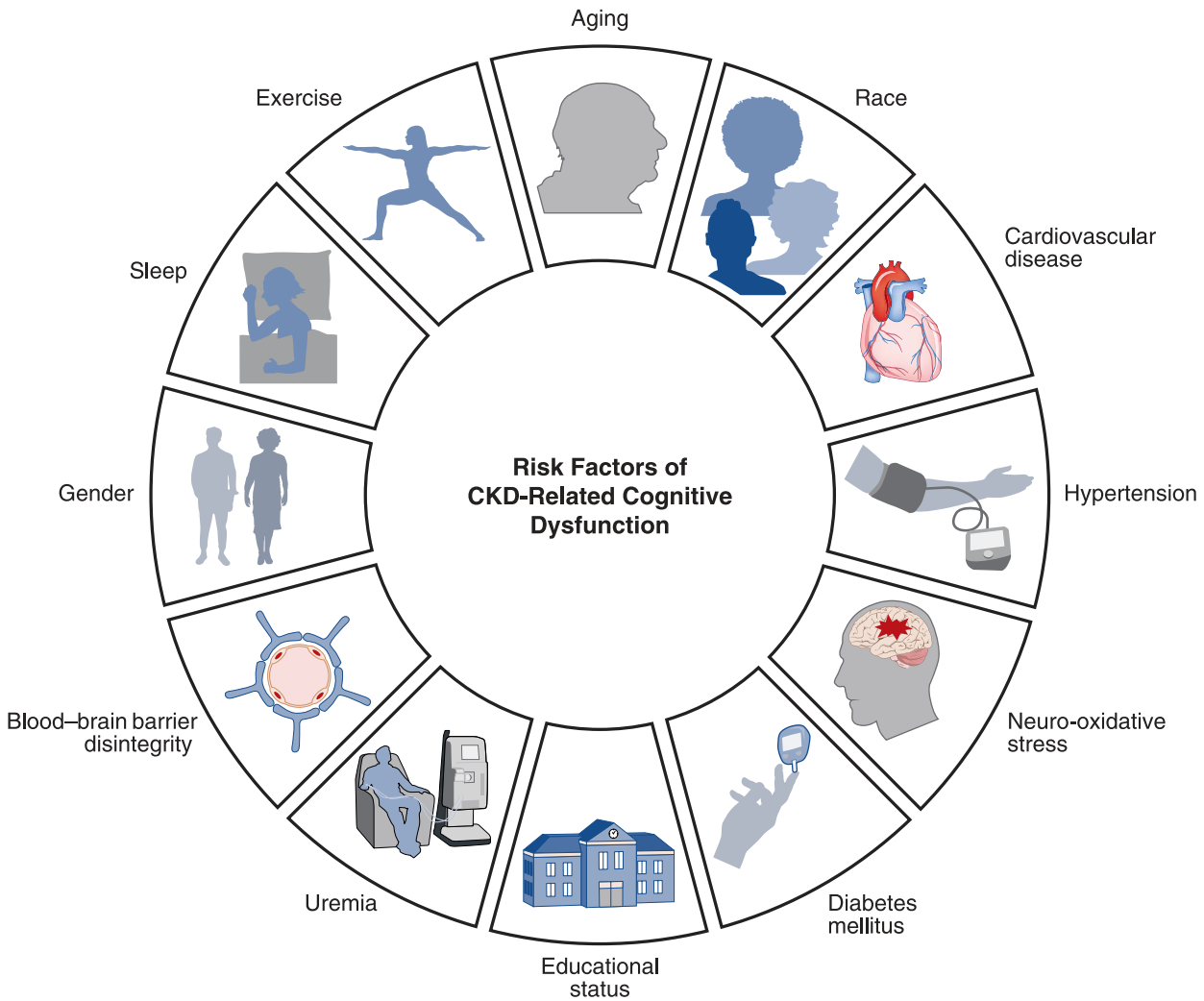

Figure 1. Various risk factors have been identified for cognitive dysfunction in CKD, including aging, race, cardiovascular disease, hypertension, neuro-oxidative stress, diabetes, educational status, uremia, blood–brain barrier disintegrity, dialysis treatments, and sex/gender. Other potential causes include sleep apnea.

in Table 1. Several studies found that cognitive impairment, as measured by validated cognitive measures and screening tools, is prevalent among individuals with reduced kidney function.[16–23] Lower eGFR, particularly eGFR <45 ml/min per 1.73 m^2, and lower kidney clearance of metabolic waste products are associated with worse performance on cognitive measures.[17,19,20,22,23] Kurella *et al.*[23] found that advanced CKD had a five-fold higher risk for global cognitive impairment and that for each 10 ml/min per 1.73 m^2 decrease in eGFR, the risk for cognitive impairment was up to 25% higher. Similarly, Shang *et al.*[24] found that CKD accelerated cognitive impairment onset by 1.24 years. A few studies did not find a relationship between eGFR and cognitive impairment or probable dementia.[25–28] However, among these, modest associations were identified for albuminuria and urine biomarkers of kidney tubule injury/dysfunction and cognitive performance.[25,26]

Dementia and CKD

Reduced eGFR and advanced CKD are associated with higher dementia incidence.[29–33] Using International Classification of Diseases-10 codes or the initiation of antidementia therapy in a registry-based cohort of over 300,000 patients (mean age 74±8 years; eGFR >15 ml/min per 1.73 m^2), Xu *et al.*[31] found that declines in eGFR were associated with higher risk of all-cause dementia and vascular dementia. Some studies observed that this relationship exists after controlling for sociodemographic covariates and factors such as ApoE genotype.[29,33] ApoE is a protein involved in cholesterol and fat movement through the bloodstream. ApoE ε4 is a known genetic risk factor for Alzheimer's disease.[34]

Cognitive Impairment and Dementia in Dialysis

Mild to severe cognitive impairment is not uncommon among dialysis-dependent patients receiving either hemodialysis or peritoneal dialysis.[35,36] In a prospective cohort study of 150 hemodialysis patients, Drew *et al.*[35] found that nearly 80% of the hemodialysis cohort had cognitive impairment (mild 17%, moderate 33%, and severe 29%), with the Montreal Cognitive Assessment (MoCA) being able to best predict severe cognitive impairment. Despite hemodynamic changes that occur during dialysis, the treatment may improve cognitive status.[37,38] However, Findlay *et al.*[37] conducted transcranial Doppler ultrasound and magnetic resonance imaging studies in nearly 100 patients and found that hemodialysis induces transient cerebral blood flow decline that correlates with intradialytic and longer-term cognitive impairment. Interestingly, Drew *et al.*[39] were unable to detect lower cognitive performance during the first hour of hemodialysis compared with the hour before dialysis start.[39] A study by Long *et al.*[30] found that the presence of a sleep disorder (26%) was associated with a risk of dementia (all cause, symptomatic Alzheimer's disease, vascular dementia, or mixed dementia) among dialysis-dependent patients (retrospective cohort of 216,000 patients). However, the use of positive airway pressure associated with a lower risk dementia. Zhu *et al.*[40] found that in elderly patients undergoing hemodialysis, age and dialysis vintage were associated with cognitive impairment. Gamage *et al.*[41] found that dialysis vintage extending beyond 12 months was associated with worse cognitive performance. In a systematic review and meta-analysis of 11 publications, which studied the effect of dialysis modality on cognitive function, a lower risk of cognitive impairment was found in peritoneal dialysis versus hemodialysis population.[42] Elgendy *et al.*[43] found that residual kidney function in patients receiving hemodialysis was associated with higher MoCA scores, suggestive of improved cognitive function in addition to better quality of life versus those without residual kidney function. Similarly, in patients receiving peritoneal dialysis, Gamage *et al.* [41] found that higher residual kidney function correlated with cognitive performance. Collectively, several dialysis-related aspects may influence cognitive function and/or dementia in patients with kidney failure.

Cognitive Impairment and Kidney Transplantation

Given that kidney transplantation restores kidney function, therein eliminating uremic toxins, and reduces risk of dialysis-associated injury, several studies have examined the prevalence and reversibility of cognitive impairment after transplantation. Gupta *et al.*[44] identified low scores on cognitive measures before kidney transplant, which subsequently improved to a level similar to age-matched healthy controls within 1 year of transplantation. Findlay *et al.*[37] found that dialysis patients receiving kidney transplant during follow-up had improved memory. Notably, Chu *et al.*[45] found that kidney transplantation associated with a 1.3-point improvement on the Modified Mini-Mental State Examination, but frailty was associated with cognitive decline. Collectively, kidney transplantation seems to positively affect CKD-associated cognitive impairment.

Uremic Toxin Effects on Brain Pathology

As kidney function diminishes, metabolic waste products or uremic toxins accumulate. Uremic toxins are generally divided into three groups: small water-soluble compounds, medium peptide compounds, and protein-bound compounds.[46] Over 100 uremic toxins have been identified.[47] In the context of kidney failure, thousands of metabolites may accumulate. Kurella *et al.*[48] conducted a metabolic profiling and identified four uremic metabolites (4-phenylacetylglutamine, phenylacetylglutamine, hippurate, and prolyl-hydroxyproline) that associated with impaired executive functioning in dialysis-dependent patients. The two most studied bacterial-derived protein-bound uremic toxins include indoxyl sulfate and p-cresyl sulfate.[47]

Indoxyl sulfate

Indoxyl sulfate is derived from dietary tryptophan that is later metabolized by intestinal microbiota into indole, which is then converted into indoxyl sulfate by the liver and ultimately eliminated by the kidney. In non-CKD patients, serum indoxyl sulfate concentration ranges between 0.1 and 2.39 μM, whereas this number can exceed 500 μM in patients with CKD.[49]

Table 1. Clinical studies evaluating cognitive dysfunction in CKD

Author, Year	Study Design	*n*	Age[a] (yr)	eGFR (ml/min per 1.73 m^2) or Dialysis Status	Follow-Up Duration	Cognitive Measures and Screening Tools	Brain Imaging	Main Findings
Shang *et al.*,[24] 2024	Longitudinal observational cohort, secondary analysis	16,515	59±10	All	7 yr (median)	Interviews by trained personnel	None	CKD accelerated cognitive impairment onset by 1.24 years
Zhang *et al.*,[16] 2024	Secondary analysis of clinical trial	105	61±12	15–44	N/A	NIH toolbox cognition battery	None	Patients with CKD scored <50th percentile across cognitive tests; CKD4 worse on cognitive measures (fluid cognition and working memory) than those with CKD3b
Long *et al.*,[30] 2024	Retrospective cohort	216,158	75 (median)	Dialysis	2 yr (mean)	Medicare claims: ICD-9/ICD-10 codes	None	Presence of a sleep disorder (26%) was associated with a higher risk of dementia (any type, Alzheimer's disease, vascular dementia, or mixed dementia); positive airway pressure use associated with a lower risk dementia
Gupta *et al.*,[100] 2023	Cross-sectional, proof-of-concept	20	49±12	Kidney failure (versus controls)	N/A	Phone-based cognitive function assessments, the National Alzheimer's Coordinating Center uniform data set telephone cognitive battery. Included MoCA blind, immediate recall, delayed recall, digit span forward, digit span backward, verbal fluency, oral trail making A, oral trail making B, category fluency for animals, category fluency for vegetables and verbal naming	^{99m}Tc-DTPA SPECT	The first study using ^{99m}Tc-DTPA SPECT to test blood–brain barrier permeability; greater blood–brain barrier permeability was found in kidney failure
Gupta *et al.*,[44] 2024	Prospective cohort	101	55±12	KT	1 yr	WMS-R logical memory 1—immediate, WMS-R logical memory 2—delayed, WAIS-R digit symbol substitution test, MMSE, digit span forward and backward, category fluency (animals, vegetables), trail making A, and trail making B	None	Before KT, controls had low scores in cognitive measures. After KT, results improved on many measures to a level similar to controls
Pépin *et al.*,[17] 2023	Prospective cohort	3033	67±13	15–60	5 yr	MMSE	None	eGFR directly correlated with MMSE score and remained significant after model adjustments
Wang *et al.*,[74] 2023	Prospective cohort	44	57±9	Hemodialysis; hemodialysis+HDF	N/A	MMSE, logical memory test-20-min delayed, verbal fluency test, digit span test, and clock drawing test	MRI	Hemodialysis+HDF patients had higher cerebral blood flow signal values in the left caudate nucleus and better verbal fluency function versus hemodialysis-only group
Dyer *et al.*,[28] 2022	Observational cohort, secondary analysis	4887	74±8	All	N/A	MMSE, FAB, and RBANS	None	Reduced eGFR associated with worse cognitive performance; strongest association with eGFR <45
Grasing *et al.*,[18] 2022	Longitudinal observational cohort, secondary analysis	1127	74±7	All	6 yr (mean)	ADNI memory: Rey auditory verbal learning test AD assessment schedule, MMSE, and logical memory data ADNI executive function: revised WAIS-R, digit symbol substitution, digit span backwards, trails A and B, category fluency and clock drawing	None	Cognitive function decreased over time in older adults across all eGFR categories; unrelated to baseline eGFR
Lidgard *et al.*,[19] 2022	Prospective cohort	2362	52±11	20–70	9.1 yr (median)	3MS	None	Lower kidney clearance of solutes associated with cognitive decline independent of baseline eGFR
Maki *et al.*,[25] 2022	Population-based, cross-sectional	8630	69±11	All	N/A	DSM-III and the Petersen criteria	T1-weighted MRI	Higher UACR associated with brain atrophy, brain structural changes, and prevalent mild cognitive impairment, while lower eGFR associated with fewer outcomes

Table 1. Continued

Author, Year	Study Design	*n*	Age[a] (yr)	eGFR (ml/min per 1.73 m^2) or Dialysis Status	Follow-Up Duration	Cognitive Measures and Screening Tools	Brain Imaging	Main Findings
Singh-Manoux *et al.*,[29] 2022	Population-based, prospective cohort	6050	66±6	All	10 yr (mean)	ICD-10	None	Decline in eGFR associated with a higher incidence of dementia, which persisted after adjustment for sociodemographic covariates and factors such as APOE ε4
Murray *et al.*,[26] 2022	Longitudinal cohort	18,131	74 (72–78)	All	4.7 yr (median)	3MS, HVLT-R, SDMT, and COWAT	None	eGFR was not associated with cognitive test performance; baseline UACR ≥3 mg/mmol (≥26.6 mg/g) associated with worse baseline function and higher risk of cognitive decline
Guerville *et al.*,[32] 2021	Secondary analysis of clinical trial	1334	75 (72–78)	All	3 yr	MMSE, free and cued selective reminding test, WAIS-R, and the category naming test	MRI	Did not identify association with brain imaging features of Alzheimer's disease with mild to moderate kidney dysfunction in community-dwelling older adults
Kashgary *et al.*,[87] 2021	Cross-sectional, multicenter cohort	241	47 (median)	Hemodialysis	N/A	MoCA	None	Did not find beneficial effects with online HDF in comparison with high-flux hemodialysis
Miller, 2021[101]	Observational cross-sectional	2253	74±9	<60	N/A	MoCA, the digit symbol coding, and logical memory 1 and 2	None	Modest association between cognitive impairment and higher concentrations of urine biomarkers of kidney tubule injury and dysfunction
Xu *et al.*,[31] 2021	Registry-based cohort	329,822	74±8	>15	5 yr (median)	ICD-10 or beginning antidementia drugs	None	As kidney function worsens, the incidence rates for dementia is higher with higher incident rates for CKD 3 or greater. Declines in eGFR were associated with higher risk of all-cause dementia and vascular dementia
Drew *et al.*,[35] 2020	Prospective cohort	150	64±14	Hemodialysis	N/A	MMSE, 3MS, MoCA, TMTB, mini-cog test, and digit symbol substitution test	None	About 79% of hemodialysis cohort had cognitive impairment (mild 17%, moderate 33%, severe 29%) with the MoCA being able to best predict severe cognitive impairment
Kurella *et al.*,[27] 2020	Secondary analysis of clinical trial	9361	60–80	All	5.1 yr (median)	MoCA and functional assessment questionnaire	None	An eGFR decline ≥30% was associated with a higher risk for probable dementia, independent of intensive treatment of hypertension
Chu *et al.*,[45] 2019	Cohort	665	52±14	KT	1.5 yr (median)	3MS	None	After transplant, cognitive impairment improved, but frailty associated with post-KT cognitive decline
Findlay *et al.*,[37] 2019	Prospective cohort	97	59 (51–67)	Hemodialysis	1 yr	MoCA, phonemic and semantic fluency, TMTA, TMTB, LDST, and HVLT	TCD ultrasound and MRI	Hemodialysis induces transient cerebral blood flow decline that correlates with intradialytic and longer-term cognitive impairment. Patients receiving KT during follow-up had improved memory and cerebral diffusion, correlating with executive function
Bai 2018[102]	Prospective cohort; double-blind placebo-controlled trial	163	83 (81–85)	>30	28 mo (median)	MMSE	None	Cognitive impairment was independently associated cardiovascular and all-cause mortality in elderly with CKD
Schneider *et al.*,[38] 2015	Prospective cohort	28	55±13	Hemodialysis	24 hr	Designed a neuropsychological test battery measuring memory, attention, executive functions, and psychomotor functions	None	64% of dialysis were cognitively impaired. Administration of a single dialysis session improved attention and long-term memory functions

Table 1. Continued

Author, Year	Study Design	*n*	Age[a] (yr)	eGFR (ml/min per 1.73 m^2) or Dialysis Status	Follow-Up Duration	Cognitive Measures and Screening Tools	Brain Imaging	Main Findings
Drew *et al.*,[39] 2013	Randomized, cross-over design; nonintervention	40	59±17	Hemodialysis	1 mo	MMSE, NAARTWMS-III word list learning subtest, the WAIS-III block design and digit symbol-coding subtests, and TMTA, TMTB, mental alternations, and COWAT	None	No evidence of lower cognitive performance associated with testing during the first hour of dialysis compared with during the hour before dialysis treatment start
Khatri *et al.*,[20] 2009	Population-based, prospective cohort	2172	72 (mean)	All	2.9 yr (mean)	TICS-m	None	Lower baseline creatinine clearance and eGFR had worse cognitive function
Hailpern *et al.*,[21] 2007	Cross-sectional	4849	20–59	30–59	N/A	Simple reaction time, symbol digit substitution, serial digit learning	None	Moderate CKD in ethnically-diverse individuals <59-yr-old was associated with poorer performance in visual attention and learning concentration. (NHANES III)
Murray *et al.*,[36] 2006	Cross-sectional	338	≥55	Hemodialysis	N/A	3MS, HVLT-R, color trails 1 and 2, stroop interference test, brief visuospatial memory test revised, COWAT, clock-drawing test, Wechsler digit span, and the geriatric depression scale (short form)	None	Cognitive impairment is common with mild (14%), moderate (36%) and severe (37%) impairment, and 13% normal cognition. Also, compared with age-matched nondialysis group
Kurella *et al.*,[22] 2005	Prospective cohort	3034	74±3	All	2 and 4 yr	3MS	None	Lower eGFR had significantly lower 3MS scores and decline in scores was greater. Severity of CKD was associated with a significant, graded risk for cognitive impairment
Kurella *et al.*,[23] 2005	Secondary analysis of randomized, blinded, placebo-controlled secondary prevention trial	1015	67±6	All	19 mo	3MS, tmt-b, modified Boston naming, verbal fluency, word list memory and word list recall	None	Across several cognitive test domains, kidney function was independent predictor of cognitive function. Advanced CKD had 5-fold higher risk for global cognitive impairment; for each 10 ml/min per 1.73 m^2 decrease in eGFR, the risk for cognitive impairment is higher by up to 25%
Seliger *et al.*,[33] 2004	Prospective cohort secondary analysis	3349	75 (mean)	All	6 yr (median)	American version of the national reading test; Raven's colored progressive matrices; California verbal learning test; Rey-Osterreith figure; immediate and delayed recall, modified Boston naming test; verbal fluency test; block design, stroop neuropsychologic screening test; trail making, digit spans, and the Baddeley Papagno divided attention task	MRI	Moderate kidney impairment was associated with higher risk of incident dementia among community-dwelling older adults

3MS, Modified Mini-Mental State; ^{99m}Tc-DTPA, radionuclide technetium Tc 99m diethylenetriaminepentaacetic acid; AD, Alzheimer's disease; ADNI, Alzheimer's Disease Neuroimaging Initiative; CI, confidence interval; COWAT, Controlled Oral Word Association Test; DSM, Diagnostic and Statistical Manual of Mental Disorders; FAB, Frontal Assessment Battery; HD, hemodialysis; HDF, hemodiafiltration; HVLT-R, Hopkins Verbal Learning Test Revised; ICD, International Classification of Diseases; IR, incidence rate; KDQOL, Kidney Disease Quality of Life; KT, kidney transplantation; LDST, Letter Digit Substitution Test; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; MRI, magnetic resonance imaging; N/A, not applicable; NAART, North American Adult Reading Test; NHANES III, Third National Health and Nutrition Examination Survey; NIH, National Institute of Health; RBANS, Repeatable Battery for Assessment of Neuropsychological Status; SDMT, Symbol Digit Modalities Test; TCD, transcranial Doppler; T-cog, National Alzheimer's Coordinating Center Uniform Data Set telephone cognitive battery; TICS-m, Telephone Interview for Cognitive Status-Modified; TMT, Trail Making Test; TMTA, Trail Making Test A; TMTB, Trail Making Test B; UACR, urine albumin-creatinine ratio; WAIS-R, Wechsler Adult Intelligence Scale-Revised; WMS-R, Wechsler Memory Scale-Revised.

[a]Age is provided as mean±SD, mean only (if SD not provided), or median based upon publication reporting.

p-Cresyl Sulfate

p-cresyl sulfate originates from dietary tyrosine (and phenylalanine) that is later metabolized by intestinal microbiota into p-cresyl, which is then converted into p-cresyl sulfate by the liver and finally eliminated by the kidney. The conjugated form of p-cresyl sulfate ($C_7H_8O_4S$) is found in the blood of patients with CKD. Using ultra-performance liquid chromatography, serum p-cresyl sulfate levels average 2.8±1.7 mg/L in patients without kidney impairment and 21.8±12.4 mg/L in patients with CKD.[49] Conventional dialysis methods (peritoneal or hemodialysis) do not effectively remove protein-bound uremic toxins typically because of the unbound fraction.[49]

Uremic toxins can enter the brain through the blood–brain barrier, in which crossing is controlled through a multiple-step and highly regulated process, that is composed of endothelial cells, astrocytes, pericytes, and the extracellular matrix.[50,51] Typically, organic anion transporter 3 shuttles protein-bound uremic toxins out of the brain and back into the blood stream. Current thinking is that in CKD, organic anion transporter 3 malfunctions lead to brain accumulation of uremic toxins.[46] Metabolic waste then interacts with brain cells such as neurons and astrocytes, affecting the veins and trafficking through the brain in individuals with reduced kidney function.[50]

Direct Effects of CKD on Alzheimer's Disease/ Alzheimer's Disease–Related Dementias

In Vitro Studies Examining CKD-Related Brain Injury

Several *in vitro* studies investigated uremic toxin effects on brain cells, emphasizing the contributions of glial activation, blood–brain barrier disintegrity, and brain oxidative stress to CKD-associated brain injury (Table 2).

Glial Activation

Zimmermann *et al.*[52] found increased IL-1β protein expression in a microglial SIM-A9 mouse cell line treated with CKD patient plasma versus controls. In a C6 rat tumor brain cell line, exposure to indoxyl sulfate led to an increase in NF-kB activation. TNF-α levels increased in the supernatant of primary mouse astrocytes and mixed glia cells treated with indoxyl sulfate.[53] In C6 rat tumor brain cell line, treatment with CKD patient plasma and with induction from LPS plus IFN led to an increase in TNF-α protein levels in the supernatant.[54] A similar trend was found in primary mouse astrocytes and mixed glia cells treated with indoxyl sulfate, wherein an increase in IL-6 protein in the supernatant was observed.[54]

Endothelia Cell Dysfunction

Zimmermann *et al.*[52] treated bEnd.3 cells with CKD patient plasma and dextran. They identified increases in barrier permeability, as seen through dextran entering the lower chamber and immunofluorescence staining. Fang *et al.*[55] found that in both human-induced pluripotent brain microvascular endothelial cells and bEnd.3 cells treated with patient plasma and gut-derived uremic toxins, there were reductions to the transendothelial electrical resistance, suggesting that there is an impaired endothelial barrier. Matsuki *et al.*[56] in bEnd.3 cells treated with urea found significant decreases in claudin-5 and CD31 and concluded that urea, through matrix metalloproteinase 2 activation, can partly regulate claudin-5 expression, thus being a player in blood–brain barrier integrity.

Oxidative Stress

Watanabe *et al.*[57] using Mouse Hippocampal Neuronal Cell Line cells found that several uremic toxins, including indoxyl sulfate, significantly decreased GSH levels. Indoxyl sulfate significantly increased the protein expression of NF (erythroid-2-related factor)-2 and mRNA expression of NADPH oxidase isoform 2 in mouse hippocampal neuronal cell line cells. Adesso *et al.*[54] found that CKD patient plasma exposure resulted in increased reactive oxygen species (ROS) in C6 cells, astrocytes, and glial cells. Adesso *et al.*[53] found that indoxyl sulfate exposure increased ROS in C6 cells, astrocytes, and mixed glial cells.

In a CKD-like environment, *in vitro* experiments induce glial activation, disintegrity to the endothelial blood–brain barrier, and oxidative stress within relevant brain cells, which may contribute to brain injury *in vivo*.

In Vivo (Animal) Studies Examining CKD-Related Brain Injury

Increasingly, knowledge of brain pathogenesis is being gained through studies involving experimental models of CKD. A variety of animal methods have been used to assess the effects of uremic toxins and reduced kidney function, which are presented in Figure 2. Collectively, these murine CKD models primarily examined oxidative stress within the brain and neuroinflammation-related outcomes, whereas a minority pursued cognitive assessments for neurobehavioral deficits or blood–brain barrier disintegrity (Table 3).

Neuroinflammation

Zimmerman *et al.*[52] used a 5/6 nephrectomy mouse model and found that brain cortices had increased activated caspase-1 and IL-1β levels versus sham mice. Fang *et al.*[55] used an adenine-rich diet CKD model in aged mice and found an increase in ionized calcium-binding adapter molecule 1 versus control mice. Sun *et al.*,[58] using unilateral nephrectomy with and without indoxyl sulfate injections, found that IL-1β was increased in the prefrontal cortical tissue in the mice treated with indoxyl sulfate. Sun *et al.*[59] in a unilateral nephrectomy model with and without p-cresyl sulfate injections found that brain-derived neurotrophic factor was decreased and that serum and prefrontal cortical tissue levels of IL-1β were increased. Reductions in brain-derived neurotrophic factor in a clinical setting are associated with many neurodegenerative diseases.[60] Adesso *et al.*[53] found that indoxyl sulfate injections significantly increased the serum levels of IL-6. Degaspari *et al.*[61] found that in a 5/6 nephrectomy in rats, only the cognitively impaired 5/6 nephrectomy rats had increased TNF-α and NF-κB binding activity in the hippocampus and frontal cortex of the brain.

Oxidative Stress

Using an adenine-rich diet, Sun *et al.*[62] found significant increases of ROS in the cerebral cortex of mice. Sun *et al.*[58] studied unilateral nephrectomy mice with and without indoxyl sulfate injections and found ROS and ROS-

Table 2. Assessment of uremic toxin or CKD effects on neurodysfunction *in vitro*

Author, Year	CKD/Uremia Injury	Cell Species	Primary versus Immortalized	Cell Type	Markers of Inflammation or Oxidative Stress	Main Findings
Zimmermann *et al.*,[52] 2024	CKD patient plasma	Mouse	Immortalized	Microglia Neuronal bEnd.3 endothelial cells	Activated (cleaved) caspase-1 and IL-1β	CKD patient plasma–induced neuroinflammation in microglial cells and blood–brain barrier impairment in endothelial cells. However, neuronal cells were not activated by CKD patient plasma
Fang *et al.*,[55] 2023	CKD patient plasma Gut-derived uremic toxins (indoxyl sulfate, p-cresyl sulfate, and TMAO)	Human Mouse	Immortalized Immortalized	Human induced BMEC bEnd.3 endothelial cells	N/A	TEER was reduced in both human induced BMEC and murine bEnd.3 endothelial cells treated with uremic toxins, urea, and LPS
Huang *et al.*,[91] 2023	I3S, FICZ, NAC CH-223191	Mouse	Primary	Astrocytes Glia-neuron Neuron-enriched	ROS	Chronic indoxyl sulfate led to reduction of GLT1 expression in astrocytes, which was reversed by CH-223191 (AhR antagonist). Chronic indoxyl sulfate did not result in increased ROS in mouse astrocytes
Matsuki *et al.*,[56] 2023	Indoxyl sulfate, TMAO, and urea	Mouse	Immortalized	Endothelial cells bEnd.3 cells	N/A	Urea, not indoxyl sulfate or TMAO, decreased claudin-5 and CD31
Watanabe *et al.*,[57] 2021	Uremic toxins (methylglyoxal, indole, IAA, indoxyl sulfate, p-cresyl sulfate, hippurate, creatinine, methylguanidine, and GSA)	Mouse	Immortalized	HT-22 cells	GSH, Nrf2 mRNA of IL-6	Uremic toxins indoxyl sulfate, methylglyoxal, IAA, and indole significantly decreased the GSH levels, an antioxidant. Indoxyl sulfate increased the expression of Nrf2, NADPH oxidase isoform 2, and IL6 in HT-22 cells
Adesso *et al.*,[54] 2018	CKD patient sera	Rat	Immortalized	C6 astrocytes	NO, TNF-α, ROS	CKD and hemodialysis patient sera increased TNF-α and NO (versus healthy control sera) in C6 cells, which was significantly reduced by AST-120. Similarly, indoxyl sulfate increased mouse astrocyte and mixed glial cell release of IL-6 and NO versus controls. Indoxyl sulfate effects were mediated through NF-kB and AhR activation in primary astrocytes and mixed glial cells
		Mouse	Primary	Astrocytes	NO, TNF-α, IL-6, ROS	
		Mouse	Primary	Glial cells	NO, TNF-α, IL-6, ROS	
Adesso *et al.*,[53] 2017	Indoxyl sulfate	Rat Mouse Mouse	Immortalized Primary Primary	C6 astrocytes Astrocytes Mixed glial cells	TNF-α, IL-6, ROS	In C6 cells treated with indoxyl sulfate, there was an increase in NF-kB activation and AhR activation. In C6 cells, astrocytes, and mixed glial cells treated with indoxyl sulfate, there was an increase in ROS

AhR, aryl hydrocarbon receptor; bEnd.3, mouse endothelial cells; BMEC, brain microvascular endothelial cells; CH-223191, AhR antagonist; FICZ, 6-formylindolo[3,2-b]carbazole, AhR agonist; GSA, guanidinosuccinate; HD, hemodialysis; HT-22, mouse hippocampal neuronal cell line; I3S, indoxyl sulfate; IAA, 3-indoleacetate; N/A, not applicable; NAC, *N*-acetylcysteine; NADPH, nicotinamide adenine dinucleotide phosphate; NO, nitric oxide; Nrf2, NF (erythroid-2-related factor)-2; ROS, reactive oxygen species; TEER, trans endothelial electrical resistance; TMAO, trimethylamine *N*-oxide; TNF-α, tumor necrosis factor-alpha.

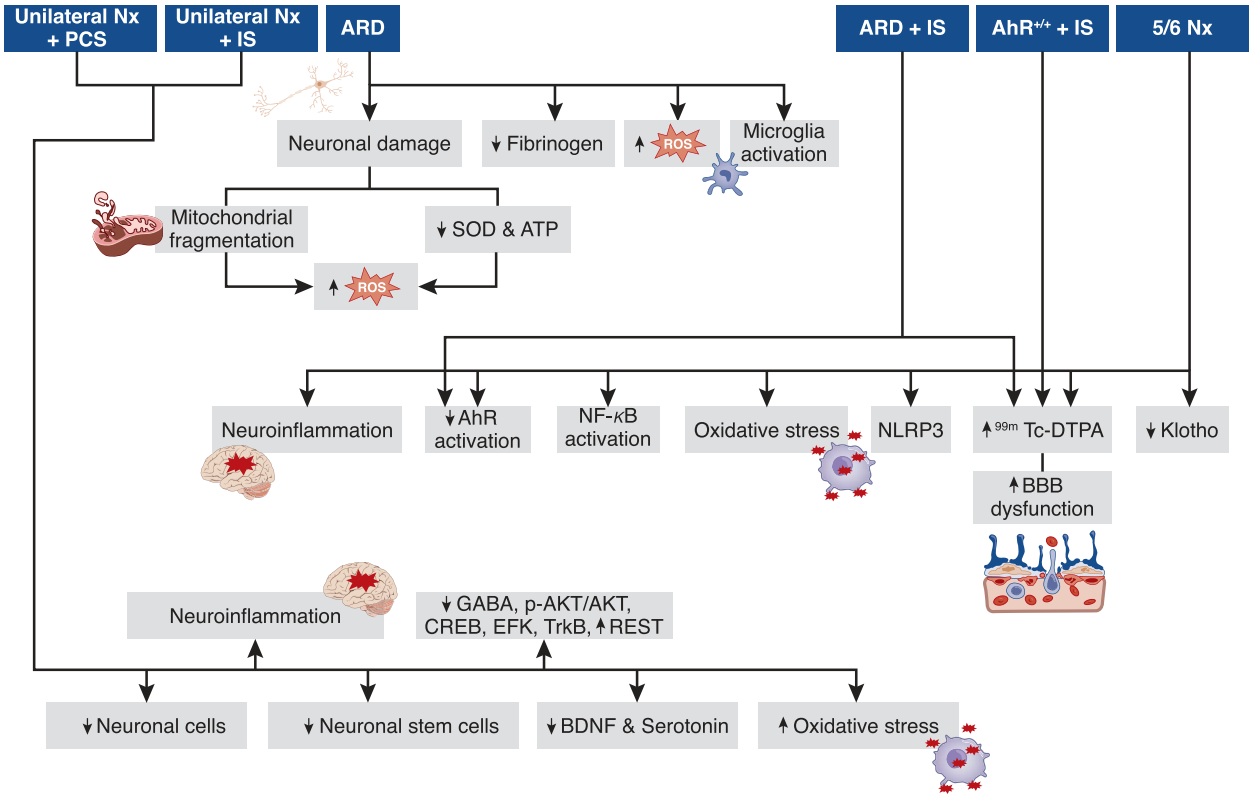

Figure 2. Using multiple CKD animal models, several pathogenic processes contributing to brain dysfunction have been identified, including mitochondrial fragmentation, microglial activation, neuroinflammation, NLRP3 inflammasome, klotho reduction, and oxidative stress. Neuronal cell damage, blood–brain barrier dysfunction, and neural stem cell loss result from these injuries. ^{99m}Tc-DTPA, radionuclide technetium Tc 99m diethylenetriaminepentaacetic acid; AhR, aryl hydrocarbon receptor; ARD, adenine rich diet; BBB, blood brain barrier; BDNF, brain-derived neurotrophic factor; CREB, cyclic AMP-responsive element-binding protein; EFK, elongation factor kinase; GABA, gamma-aminobutyric acid; IS, indoxyl sulfate; NF-kB, nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP3, NOD-, LRR-, and pyrin domain–containing protein 3; Nx, nephrectomy; p-AKT/AKT, protein kinase B; PCS, paracresyl sulfate; REST, repressor element-1 silencing transcription factor; ROS, reactive oxygen species; SOD, superoxide dismutase; TrkB, tropomyosin receptor kinase B or tyrosine receptor kinase B.

related species in prefrontal cortical tissues. When Sun *et al.*[59] applied unilateral nephrectomy with or without administration of p-cresyl sulfate, ROS were observed in the prefrontal cortex of the p-cresyl sulfate mice. Fujisaki *et al.*[63] using a 5/6 nephrectomy model found increased 8-hydroxyguanosine immunoreactivity in the nuclei of hippocampal cornu ammonis 3 neurons. Similar findings were reported by Haruyama *et al.*[64]

Neurobehavioral Deficits

Zimmermann *et al.*[52] in a 5/6 nephrectomy CKD mouse model identified cognitive deficits compared with age-matched and sex-matched sham controls. Spatial working memory deficits were observed by Matsuki *et al.*[56] after administering adenine-rich diet for 6 weeks. Using a 5/6 nephrectomy CKD mouse model, Li *et al.*[65] found increased indoxyl sulfate in several brain regions and working memory deficits. Sun *et al.*[58] observed behavioral abnormalities in unilateral nephrectomy mouse model with and without indoxyl sulfate injections. Bobot *et al.* [66] found that rats receiving an adenine-rich diet had significant cognitive deficits. Sun *et al.*[59] studied unilateral nephrectomized mice with or without p-cresyl sulfate administration and identified several neurobehavioral abnormalities. Both Fujisaki *et al.*[63] and Haruyama *et al.*[64] identified spatial working memory impairment in CKD mice.

Blood–Brain Barrier Disintegrity

Zimmermann *et al.*[52] in 5/6 nephrectomy mice found increased amount of Evans Blue dye in the brain tissue versus controls, suggesting increased blood–brain barrier permeability. Matsuki *et al.*[56] in mice fed an adenine-rich diet for 6 weeks found diffuse IgG in the subendothelial area of the hippocampus parenchyma, suggestive of a weakened blood–brain barrier. Bobot *et al.*[66] in both rats fed an adenine-rich diet and in those undergoing 5/6 nephrectomy had higher levels of radionuclide technetium Tc 99m diethylenetriaminepentaacetic acid in the brain. Radionuclide technetium Tc 99m diethylenetriaminepentaacetic acid is used as a marker of blood–brain barrier permeability because in normal physiologic conditions, it cannot cross the blood–brain barrier.

Indirect Effects of CKD on Alzheimer's Disease/ Alzheimer's Disease–Related Dementias

Patients with CKD have an estimated 1.14-fold higher risk of developing Alzheimer's disease dementia as defined by

Table 3. Assessment of neurodysfunction in CKD animal models

Author, Year	Age	Species, Sex, Background	CKD/Uremic Injury Model	Uremic Toxin Measured (Source)	Markers of Inflammation or Oxidative Stress	Neurobehavioral Tests	Main Findings
Zimmermann *et al.*,[52] 2024	6- to 8-wk-old	Mouse Not reported C57BL/6	5/6 nephrectomy	N/A	Caspase-1, IL-1β	Nonspatial object recognition test and the radial arm maze	5/6 nephrectomy mice had cognitive impairment suggested by learning and memory deficits
Matsuki *et al.*,[56] 2023	7- to 8-wk-old	Mouse Males only C57BL/6JJcl	0.2% adenine diet for 6 wk Normal chow for 13 d, 0.2% adenine for 2 d Normal chow for 7 d, 0.2% adenine for 8 d 0.2% adenine for 15 d 5/6 nephrectomy	N/A	N/A	NOR, Y-maze spontaneous alterations test	CKD mice had loss of spatial working memory CKD mice had blood–brain barrier dysfunction because of diffuse IgG in the brains, subendothelial area of hippocampus parenchyma Tight junction proteins and adherent junction proteins were decreased in CKD Early stages of kidney dysfunction induced blood–brain barrier dysfunction
Huang *et al.*,[91] 2023	8-wk-old	Mouse Males only C57BL/6 nAhRCKO aAhRCKO	5/6 nephrectomy	Indoxyl sulfate (brain homogenates and plasma)	GFAP ROS NAC	OFT, NOR, EPM	CKD led to indoxyl sulfate brain deposition, neurobehavioral deficits, and AhR activation in brains (anterior cortex) versus controls. Conditional knockout (astrocytic and neuronal) of AhR ameliorated GFAP positive astrocytes and glutamate transporter-1 in the anterior cingulate cortex
Fang *et al.*,[55] 2023	17-mo-old	Mouse Males and females C57BL/6J	0.2% adenine diet for 18 d, regular chow for 2 wk, then 0.2% adenine diet for 1 wk	N/A	IBA-1 in microglia and GFAP in astrocytes (IHC)	N/A	Increased IBA-1 positive microglia in comparison with controls. No difference between GFAP astrocytes in controls versus CKD
Sun *et al.*,[62] 2022	8-wk-old	Mouse Males only C57BL/6J	0.2% adenine diet for 6 wk	N/A	ROS levels *via* DHE staining SOD activity contents of MDA and ATP	N/A	Increased ROS and MDA with concurrent significant decreases in ATP and SOD in the cerebral cortex of the CKD mice
Sun *et al.*,[58] 2021[a]	10-wk-old	Mouse Males only C57BL/6	Unilateral nephrectomy with or without intraperitoneal indoxyl sulfate	Indoxyl sulfate (prefrontal cortical tissues, serum, and CSF)	MDA IL-1β 8-OHdG	Modified-OFT, FST, TST, light-dark box test, and MWM	IL-1β upregulated in the PFC, serum, and cortical tissues MDA and 8-OHdG were increased in prefrontal cortex Behavioral abnormalities suggestive of cognitive impairment
Li *et al.*,[65] 2021	8-wk-old	Mouse Males only C57BL/6J	5/6 nephrectomy	Indoxyl sulfate and p-cresyl sulfate (serum, frontal lobe, hippocampus, cerebellum, basal ganglion)	IL-1β, IL-18, and caspase-1	Y-maze spontaneous alternation test and MWM	Indoxyl sulfate and p-cresyl sulfate significantly increased in serum after injury All inflammatory markers were increased in the hippocampus Behavioral abnormalities suggestive of cognitive impairment in both neurobehavioral assessments
Bobot *et al.*,[66] 2020[b]	5-wk-old 5-wk-old 5-wk-old	Rats Males only Sprague–Dawley Rats Males only Sprague–Dawley Rats Males only Sprague–Dawley	5/6 nephrectomy 0.25% adenine diet for 28 d 0.5% adenine diet for 28 d with indoxyl sulfate (drinking water) added at day 14 for 14 d	Indoxyl sulfate (serum, CSF) p-cresyl sulfate, indole acetic acid (CSF)	N/A	NOR, object location	Indoxyl sulfate increased in serum and CSF after injury Blood–brain barrier permeability increased postinjury Positive correlation with indoxyl sulfate levels and blood–brain barrier permeability Neurobehavioral abnormalities suggestive of cognitive impairment

Table 3. Continued

Author, Year	Age	Species, Sex, Background	CKD/Uremic Injury Model	Uremic Toxin Measured (Source)	Markers of Inflammation or Oxidative Stress	Neurobehavioral Tests	Main Findings
	5-wk-old	Rats Males only Sprague–Dawley	0.5% adenine diet for 28 d				
	Not available	Mouse Sex not reported B6.129-Ahr^{tm1Bra}/J	AhR knockout mice with or without indoxyl sulfate (drinking water) for 14 d				
Sun *et al.*,[59] 2020[c]	10-wk-old	Mouse Males only C57BL/6	Unilateral nephrectomy with or without p-cresyl sulfate intraperitoneal	p-cresyl sulfate (serum, prefrontal cortical tissue)	IL-1β MDA 8-OHdG	OFT, FST, TST, light-dark box test, and MWM	The 100 mg/kg per day p-cresyl sulfate group were found to have behavioral abnormalities suggestive of cognitive impairment. Oxidative stress levels increased in PFC. BDNF was decreased IL-1β increased in serum and PFC
Adesso *et al.*,[53] 2017[d]	6- to 8-wk-old	Mouse Females only C57BL/6	Indoxyl sulfate intraperitoneal	Indoxyl sulfate (serum)	TNF-α and IL-6	N/A	Indoxyl sulfate led to increased IL-6 in serum
Degaspari *et al.*,[61] 2015	2-mo-old	Rats Males only Munich–Wistar	5/6 nephrectomy	N/A	TNF-α, IL-10, IL-1β, IL-6, IFN-γ, CRP and GC	Inhibitory avoidance, NOR, locomotor activity test	Only cognitively impaired 5/6 Nx rats had increased TNF-α and NF-κB binding activity in the hippocampus and frontal cortex of brain Oxidative stress evident in cerebellum of 5/6 Nx mice
Fujisaki *et al.*,[63] 2014	8-wk-old	Mouse Males only C57BL/6J	5/6 nephrectomy	N/A	8-OHdG	RAWM, open field testing	Increased 8-OHdG immunoreactivity in the nuclei of hippocampal CA3 neurons Deficits in the RAWM led to the conclusion that spatial working memory is impaired
Haruyama *et al.*,[64] 2014	8-wk-old	Mouse Males only C57BL/6J	5/6 nephrectomy with or without telmisartan	N/A	Malondialdehyde, 8-OHdG (IHC)	RAWM	Higher amounts of 8-OHdG in the CA3 region of the hippocampus Increased errors in RAWM testing suggestive of impaired working memory

8-OHdG, 8-hydroxyguanosine; aAhrCKO, astrocyte-specific Ahr conditional knockout mice; AhR, aryl hydrocarbon receptor; BDNF, brain-derived neurotrophic factor; CA3, cornu ammonis 3; CRP, C-reactive protein; CSF, cerebral spinal fluid; DHE, dihydroethidium; EPM, elevated plus maze; FST, forced swim test; GC, glucocorticoid; GFAP, glial fibrillary acidic protein; IBA-1, ionized calcium-binding adapter molecule 1; IHC, immunohistochemistry; IS, indoxyl sulfate; MDA, malondialdehyde; MWM, Morris water maze; N/A, not applicable; NAC, *N*-acetyl-l-cysteine; nAhrCKO, neural lineage-specific Ahr conditional knockout mice; NF-κB, nuclear factor-kB; NOR, novel object recognition; Nx, nephrectomy; OFT, open field test; PCS, paracresyl sulfate; PFC, prefrontal cortex; RAWM, radial arm water maze; ROS, reactive oxygen species; TNF-α, tumor necrosis factor-alpha; TST, tail suspension test.

[a]For dose effect studies, intraperitoneal indoxyl sulfate was administered at 0, 1, 10, and 100 mg/kg per day for 7 weeks. For intervention studies, intraperitoneal indoxyl sulfate was administered at 100 mg/kg per day for 7 weeks.

[b]For dose effect studies, intraperitoneal p-cresyl sulfate was administered at 0, 1, 10, and 100 mg/kg per day for 7 weeks. For intervention studies, intraperitoneal p-cresyl sulfate was administered at 100 mg/kg per day for 7 weeks.

[c]Indoxly sulfate was placed in the drinking water during days 14–28 (1 g of indoxyl sulfate per liter of water).

[d]Single intraperitoneal indoxyl sulfate dose was administered at 800 mg/kg.

International Classification of Diseases.[67] Several factors may underpin this higher risk, such as aging and cerebral small vessel disease. Cerebral small vessel disease, which has been implicated in cognitive impairment, includes pathologic, clinical, and radiologic cerebrovascular changes.[68] Inflammatory and immunologically mediated cerebral small vessel disease is presented by a surplus immune cell permeation into vessel walls from systemic inflammation.[68] Systemic low-grade inflammation has been well established in CKD. In fact, the role of inflammation is well implicated in CKD progression and has been well reviewed previously.[69] The most common risk factors for CKD, and CKD cognitive impairment, such as age, hypertension, and diabetes, are also common risk factors for cerebral small vessel disease.[11,68] Interestingly, both CKD and Alzheimer's disease have been implicated with vascular cognitive impairment and disproportionately affect certain populations, including the elderly, women, and Black Americans.[1,70–73]

Scheppach *et al.*[71] found that eGFR and albuminuria were associated with structural brain damage. However, this damage was not in regions typically associated with Alzheimer's disease. They also determined that patients with lower eGFR have higher volume of white matter hyperintensities, a sign of cerebral small vessel disease, thus in alignment with previous reports.[71,72] Vascular cognitive impairment is an umbrella term relating to any vascular brain pathology resulting in cognitive impairment. One of the main cerebrovascular pathologies in vascular cognitive impairment are white matter hyperintensities. Indeed, patients with CKD have increased white matter hyperintensity volumes as detected by fluid-attenuated inversion recovery magnetic resonance imaging.[72] Cerebrovascular disease often coexists with Alzheimer's disease, particularly in older patients.[73]

Alzheimer's disease/Alzheimer's disease–related dementias neuropathology and rates of cognitive decline are exacerbated in individuals with CKD plus Alzheimer's disease/Alzheimer's disease–related dementias. Wang *et al.*[74] found that the onset of dementia/Alzheimer's disease–related dementia was 1.71 years quicker in those with impaired kidney function versus those without. A higher prevalence of dementia and Alzheimer's disease–related dementia was found in those with eGFR <73.3 ml/min per 1.73 m^2. Cerebral amyloid angiopathy likelihood was much higher in those with eGFR <59.5 versus ≥73.3 ml/min per 1.73 m^2. Using a familiar Alzheimer's disease with 5 Alzheimer's disease linked mutations mouse model of Alzheimer's disease, which presents with main features of Alzheimer's disease, and addition of adenine-rich diet, Nakagawa *et al.*[75] found that cognitive impairment was worsened in Alzheimer's disease-CKD mice versus Alzheimer's disease mice as measured by the Morris water maze test. In addition, cerebral IgG leakage was more pronounced in Alzheimer's disease-CKD versus Alzheimer's disease mice. In patients from the Japanese Alzheimer's Disease Neuroimaging Initiative, Iwata *et al.*[76] found that decreasing kidney function was associated with higher rate of cognitive function decline. Collectively, cognitive impairment effects are likely compounded in patients with brain dysfunction from other processes—particularly Alzheimer's disease/Alzheimer's disease–related dementias, in which vascular changes are already presumed to contribute. The ultimate effects of this "double hit" may be additive or multiplicative, compounding neurodegeneration, accelerating cognitive declines, and compromising cognitive outcomes.

Therapeutic Interventions to Improve CKD-Associated Cognitive Impairment

In Animal and Cell Models

A multitude of *in vitro* and *in vivo* studies has tested the efficacy of AST-120 (a charcoal adsorbent), CH-223191, triarylmethane-34, anakinra, and marimastat for their abilities to ameliorate CKD-induced central nervous system damage. These studies, summarized in Table 4, provided additional mechanistic insights and were the foundation for subsequent drug development for testing in human clinical trials.

In Humans

Several clinical trials (and prospective studies) assessed the effect of various interventions on CKD-associated cognitive impairment (Table 5). Collectively, these interventions included exercise, B vitamins, AST-120, valerian (agonist of adenosine A1 receptors), and thiamin plus folic acid. Of note, despite promising preclinical intervention studies in animal models, small sample size and end point selection may have contributed to reduced efficacy observed in the human clinical trials.

Exercise Interventions

Exercise-associated beneficial effects on cognitive function in CKD may be attributed to reduction in cardiovascular and cerebrovascular disease risk factors that also contribute to cognitive impairment such as insulin resistance, high BP, arterial stiffness, reduced quality of life, obesity, and depression, as previously reviewed by Bradshaw *et al.*[77] Otobe *et al.*[78] used several cognition measures: Mini-Mental State Exam, Wechsler Memory Scale-Revised Logical Memory, the Trail Making Test parts A and B, and the verbal fluency test with findings that a 26-week exercise intervention improved memory function in older adults (n=81; eGFR 15–59 ml/min per 1.73 m^2) versus controls. Similarly, Sheshadri *et al.*[79] implemented a 3-month pedometer-based exercise intervention for patients (n=30) on dialysis (hemodialysis or peritoneal), assessed cognitive status through the Telephone Interview for Cognitive Status (TICS), and found an association between worse TICS results and reduced benefits of the intervention in comparison with noncognitively impaired participants.

AST-120

AST-120 lowers indoxyl sulfate levels through intestinal binding of indole and is the most well-studied intervention for uremic toxin removal. Cha *et al.*[80] in a randomized controlled, parallel group, open-label, multicenter trial administered AST-120 to predialysis CKD patients (n=150). AST-120 increased kidney function and cognitive function (cognitive measures were not described). Although AST-120 has received approval for delaying CKD progression in several Asian countries, it is currently not approved for use in the United States. The last published clinical trial in the

Table 4. Interventions to reduce uremic toxin/CKD effects in CKD models

Author, Year	CKD Model	Treatment	Main Findings
***In vivo* studies**			
Zimmermann *et al.*,[52] 2024	5/6 Nx in C57BL/6 and 5/6 Nx in EmxCre×IL1R1LoxP/LoxP mice (IL1RΔN mice)	TRAM34 and anakinra	Prevention of microglia activation by suppressing microglia potassium efflux through TRAM34 allowed for rescue in memory in 5/6 Nx mice In mice without IL-1R1 in their neurons (IL1RΔN mice), there was augmentation of cognition Anakinra (IL-1R inhibitor) treatment in 5/6 Nx mice resulted in improved cognition
Huang *et al.*,[91] 2023	5/6 Nx in C57BL/6, $ahr^{flx/flx}$, nAhrCKO and aAhrCKO mice	CH-223191	Conditional AhR KO mice experienced reductions in anxiety-related responses versus $Ahr^{flx/flx}$-CKD mice CH-223191 (an AhR antagonist) treatment led to reductions in astrogliosis and memory impairment
Li *et al.*,[65] 2021	5/6 Nx on C57BL/6J and NLRP3-knockout mice	AST-120	AST-120 led to reduced indoxyl sulfate in the frontal lobe and hippocampus, aided in reversing learning and memory deficits, and reduced neuroinflammation in the hippocampus. NLRP3-knockout mice induced with CKD showed no cognitive impairment
Sun *et al.*,[58] 2021	Unilateral Nx or unilateral Nx with indoxyl sulfate injections in C57BL/6 mice	AST-120	AST-120 led to reduced indoxyl sulfate levels in blood, prefrontal cortex, and CSF AST-120 ameliorated abnormal behavioral changes, encouraged neuronal cell survival, and reversed the upregulation in oxidative stress neuroinflammation. BDNF and serotonin reductions were also reversed by AST-120 treatment
Bobot *et al.*,[66] 2020	0.5% adenine-rich diet in Sprague–Dawley rats. $AhR^{-/-}$ knockout given indoxyl sulfate	AST-120	AST-120 reduced serum indoxyl sulfate levels and did not alter blood–brain barrier permeability measures. $AhR^{-/-}$ knockout mice seemingly resistant to cognitive disturbances and blood–brain barrier disruptions
Sun *et al.*,[59] 2020	Unilateral (1/2) Nx on C57BL/6 mice $^{+/-}$ p-cresyl sulfate injections	AST-120	AST-120 led to reduced p-cresyl sulfate levels in the serum and prefrontal cortex, amelioration in abnormal behavioral changes, attenuated deficits in neural stem cell and neuronal cells, BDNF and reversed serotonin reductions, reversed increased oxidative stress, and ameliorated neuroinflammation
Haruyama *et al.*,[64] 2014	5/6 Nx in C57BL/6 J male mice	Telmisartan	Telmisartan reduced 8-OHdG in the CA3 region of the hippocampus and malondialdehyde concentrations. Telmisartan treatment contributed to the alleviation of neurobehavioral abnormalities
***In vitro* studies**			
Zimmermann *et al.*,[52] 2024	SIM-A9 CKD patient plasma	TRAM34	Prevention of microglia activation *via* suppressing microglia potassium efflux through TRAM34 showed reduction of potassium efflux from CKD plasma treatment, soma width, IL-1β, and phosphorlated-p38
Huang *et al.*,[91] 2023	Primary mouse astrocytes with indoxyl sulfate	CH-223191	Reduction in AhR activation and GLT1 protein levels after treatment with AhR antagonist in chronic indoxyl sulfate conditions
Matsuki *et al.*,[56] 2023	bEnd.3 cells with indoxyl sulfate, TMAO, and urea	Marimastat	Treatment with a MMP inhibitor partially rescued claudin-5 expression when also treated with urea, which is suggestive that urea through MMP-2 activations partially controls claudin-5 expression
Adesso *et al.*,[54] 2018	Immortalized C6 astrocytes in 2% patient plasma	AST-120	AST-120 reduced ROS in C6 astrocytes in both inflammatory and normal conditions. In addition, AST-120 led to reductions in NO and TNF-α in C6 astrocytes

8-OHdG, 8-hydroxyguanosine; aAhrCKO, astrocyte-specific Ahr conditional knockout mice; AhR, aryl hydrocarbon receptor; BDNF, brain-derived neurotrophic factor; bEnd.3, mouse endothelial cells; CA3, cornu ammonis 3; CSF, cerebral spinal fluid; GLT1, glutamate transporter-1; IL-1R, IL-1 receptor; KO, knockout; MMP, matrix metalloproteinases; nAhrCKO, neural lineage-specific Ahr conditional knockout mice; NLRP3, NOD-, LRR-, and pyrin domain–containing protein 3; NO, nitric oxide; Nx, nephrectomy; SIM-A9, microglial cell line derived from mouse pups' cerebral cortex tissue; TMAO, trimethylamine *N*-oxide; TNF-α, tumor necrosis factor-alpha; TRAM34, triarylmethane-34.

Table 5. Clinical trials interventions in patients with CKD

Author, Year	Clinical Trial Design	*n*	Age (yr)	eGFR (ml/min per 1.73 m^2) or Dialysis Status	Study Intervention (Duration)	Cognitive Function Measures; Screening Tool	Main Findings
Exercise interventions							
Otobe *et al.*,[78] 2021	Randomized, controlled, single-center, unblinded, and stratified	81	79±6	15–59	Exercise versus control (24 wk)	MMSE, WMS-RLM, TMT	WMS-RLM memory delayed recall and immediate and delayed recall scores had significant change in exercise versus control group
Sheshadri *et al.*,[79] 2021	Randomized, controlled, multicenter	30	60 (median)	Kidney failure (hemodialysis, PD)	Pedometer-based walking versus control (3 mo)	TICS	Lower cognition function at baseline was associated with less improvement in exercise performance
Drug and supplement interventions							
Cha *et al.*,[80] 2022	Randomized, controlled, multicenter, parallel group, open-label	150	65±11	15–60	AST-120 (Renamezin) versus placebo (48 wk)	KDQOL (cognitive function)	Cognitive function and kidney function and improved in the AST-120 versus placebo group
Brady *et al.*,[83] 2009	Randomized controlled, multicenter, double-blind	659	63±12	eGFR ≤30 and kidney failure	High-dose B vitamins versus placebo (5 yr)	TICS-m	No difference in TICS-m cognitive outcomes between groups
Samaei *et al.*,[84] 2018	Randomized, crossover, double-blind	39	66±14	Kidney failure ≥3 mo of hemodialysis	Valerian versus placebo (2 mo; one mo with drug and 1 mo placebo)	MMSE	Cognitive score increases were higher in the valerian-treated group versus placebo
Lu *et al.*,[82] 2021	Randomized, controlled, single-center	50	66±8	Kidney failure ≥3 mo of hemodialysis	Thiamin plus folic acid versus control (96 wk)	MoCA (score <26 for inclusion)	MoCA score increases were higher in the thiamin plus folic acid group versus control
Dialysis-related interventions							
Dasgupta *et al.*,[86] 2024	Randomized, controlled, multicenter, feasibility	43	68 (median)	Kidney failure (hemodialysis)	Cooled dialysate versus control (12 mo)	MoCA	High attrition rate during COVID-19 pandemic. Low temperature dialysis was well tolerated. No difference in change in MoCA for cooled versus standard group at 12 mo
Rose *et al.*,[89] 2024	Randomized, controlled, multicenter	1360	62±14	Kidney failure ≥3 mo of hemodialysis	High-dose HDF versus high-flux hemodialysis (24 mo)	Four-item PROMIS cognitive function short form	Cognitive function declined twice as fast for the hemodialysis group versus the HDF group (−1.05 versus −0.49 units/yr)
Lim *et al.*,[90] 2020	Randomized, prospective, controlled, open-label	49	62±14	High-flux membrane hemodialysis ≥3 mo	Medium cut-off dialyzers versus hemodialysis (12 wk)	KDQOL (cognitive function)	No difference in cognitive function at baseline or 12 wk into the intervention

COVID-19, coronavirus disease 2019; HDF, hemodiafiltration; KDQOL, Kidney Disease Quality of Life; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; PD, peritoneal dialysis; PROMIS, Patient-Reported Outcomes Measurement Information System; TICS, Telephone Interview for Cognitive Status; TICS-m, Telephone Interview for Cognitive Status-Modified; TMT, Trail Making Test; WMS-RLM, Wechsler Memory Scale-Revised Logical.

United States to evaluate AST-120 was the Evaluating Prevention of Progression in CKD trial. Schulman *et al.*[81] treated patients (n=2000) with moderate to severe CKD and found no beneficial effect of AST-120 on slowing the progression of CKD.

Vitamins and Herbal Supplement Interventions

Lu *et al.*[82] implemented a thiamine and folic acid intervention in patients (n=50) with kidney failure and cognitive impairment in a randomized, controlled, single-center study and measured their cognitive status through MoCA. Patients treated with thiamin and folic acid had improved MoCA scores. In a 5-year multicenter randomized double-blind placebo-controlled trial in patients (n=659) with advanced CKD or kidney failure, Brady *et al.*[83] administered high-dose B vitamins but did not witness differences in cognitive outcomes as measured by the modified TICS. In a randomized, crossover, double-blind clinical trial, Samaei *et al.*[84] used valerian, an herbal product, in hemodialysis patients (n=39) and found that 1-month administration of valerian significantly improved cognitive function as assessed by the Mini-Mental State Exam.

Dialysis-Related Interventions

Given the occurrence of intradialytic hypotension during hemodialysis, studies have examined the effect of dialysate cooling on cerebrovascular changes.[85] Dasgupta *et al.*[86] conducted a feasibility randomized control trial aimed to assess the effects of cooling dialysate on cognitive function in patients (n=43) with kidney failure. Unfortunately, the study was affected by the coronavirus disease 2019 pandemic, leading to high attrition rate (27%). Low temperature dialysis (35°C versus 36.5°C) was well tolerated, but no differences were observed between groups for change in MoCA from baseline to 12 months. Other clinical studies have examined the effect of hemodiafiltration on cognitive function. Kashgary *et al.*[87] found no cognitive outcome differences in patients (n=241) receiving online hemodiafiltration versus high-flux hemodialysis in a cross-sectional, multicenter cohort study. However, Wang *et al.*[88] in a prospective cohort study of patients (n=44) with kidney failure found that those receiving hemodiafiltration plus hemodialysis had better verbal fluency cognitive measure versus hemodialysis. In a randomized controlled clinical trial (comparison of high-dose hemodiafiltration with high-flux hemodialysis), Rose *et al.*[89] found that cognitive function declined twice as fast for patients (n=1297) undergoing high-flux hemodialysis versus the high-dose hemodiafiltration (–1.05 versus –0.49 units/yr) as evaluated within quality of life measures. In an assessment of dialyzers, Lim *et al.*[90] conducted a randomized, prospective open-label phase 4 trial applying medium cutoff and high-flux dialyzers. They also investigated effects on cognitive function using quality of life outcomes in hemodialysis patients (n=49) and found no significant difference between groups.

Considerations for Future Kidney–Brain Axis Investigations and Treatment

Thus far, clinical trials testing therapeutics, beyond kidney transplantation and potentially high-dose hemodiafiltration, in humans have produced limited improvement in cognition in patients with CKD. Additional investigations are needed to enhance understanding of the kidney-brain axis.

Cellular Senescence

Cellular senescence is a process in which cells no longer proliferate due to arrest in the cell cycle G1 phase and has a pivotal role in CKD pathogenesis.[91] Senescent cells develop a senescence-associated secretory phenotype that propagates local and systemic inflammation.[91] A study examined the prosenescence effects of protein-bound uremic toxins in CKD-animal models.[92] Although cellular senescence has beneficial effects, an increase in senescent cell accumulation can be found in CKD states, brain aging, and neurodegeneration. We conducted a phase 1 clinical trial testing senolytics (dasatinib and quercetin) in older individuals with diabetes and CKD.[93] We demonstrated, for the first time in humans, that senolytics clear senescent cells in adipose tissue and skin while reducing systemic proinflammatory markers.[93] Several early phase clinical trials applying senolytics in Alzheimer's disease and cognitive impairment are ongoing (NCT04063124; NCT04785300).[94] The interaction between neurosenescence in patients with cognitive impairment due to Alzheimer's disease/Alzheimer's disease–related dementias and CKD is unknown and should be further investigated. Furthermore, senotherapeutics may aid in improvement of multiple organ systems altered in CKD.

Alternative CKD Animal Models

Animal models to investigate cognitive impairment in CKD have been primarily limited to young adult mice with CKD induced through diet, surgery, and/or uremic toxin injections. Future studies could diversify by incorporating models typically used in Alzheimer's disease/Alzheimer's disease–related dementias research. In addition, aged CKD models may improve translatability given age distribution in human CKD. Further studies may allow for age-based difference assessments in CKD-associated cognitive impairment.

Regenerative Therapies

Regenerative, cell-based therapies have been investigated for the treatment of multiple kidney diseases. The US Food and Drug Administration approved the first mesenchymal stromal cell therapy Ryoncil, an allogeneic bone marrow–derived mesenchymal stromal cell, for pediatric steroid-refractory acute graft-versus-host disease.[95] We and others are conducting clinical trials testing the safety and early efficacy signals of mesenchymal stem cells in patients with CKD (NCT05362786; NCT04869761; NCT06752577).[96] Cell-based therapies, such as extracellular vesicles and exosomes, may be administered intranasally and an early phase clinical trial suggested safety and tolerability in patients with Alzheimer's disease.[97] Mesenchymal stem cell–derived extracellular vesicles may assist in reduction of vascular dementia through their proliferation, tube formation, and proangiogenesis factors.[98] We have shown that the delivery of induced mesenchymal stromal cells into a mouse model of acute brain injury ameliorated

neuronal injury through restored synaptic metabolic activity.[99] Future development of therapeutic strategies adapting both systemic and intranasal delivery of extracellular vesicles in patients with CKD with cognitive impairment may lead to improvement in multiple organ systems and reduced morbidity.

Conclusions

Cognitive impairment is common in patients with CKD. Multiple factors associated with CKD are also associated with Alzheimer's disease/Alzheimer's disease–related dementias. The accumulation of uremic toxins and dialysis procedure may induce brain cell injury, diminish brain perfusion, and contribute to cognitive decline. Although kidney transplantation may restore impairments found in dialysis-dependent patients, frailty may nullify this potential benefit. Cell and animal models provide unique insights into the contributions of uremic toxins, organic anion transporters, and inflammatory pathways leading to neuroinflammation (activated microglia), oxidative stress within the brain, blood–brain barrier integrity, and neurobehavioral abnormalities. Promising interventions in murine CKD models have not been replicated in human studies. However, exercise and potentially high-dose hemodiafiltration have modest effects in dialysis-dependent patients. It is likely that additional pathogenic processes such as cellular senescence burden in the brain may be an untreated and underrecognized contributor to CKD-associated cognitive impairment. Senotherapeutics and regenerative products should be further explored given anti-inflammatory properties that may affect the kidney-brain axis. Although further studies are needed, the abundance of investigations in recent years has provided immense knowledge and forge the path to improve the lives of patients affected by CKD and cognitive impairment.

Disclosures

Disclosure forms, as provided by each author, are available with the online version of the article at http://links.lww.com/JSN/F100.

Funding

L.J. Hickson: National Institutes of Health. G.S. Day: National Institutes of Health (R01AG089380, U01AG057195, U01NS120901, and U19AG032438). T. Kanekiyo: National Institutes of Health (U19AG069701, R01AG071226, R01AG068034, R01AG081203, and RF1AG057181). S.R. Irani: Medical Research Council (MR/V007173/1), Wellcome Trust Fellowship (104079/Z/14/Z), National Institute for Health Research (NIHR) Oxford Biomedical Research Centre (BRC).

Acknowledgments

The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR, or the Department of Health.

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T. Andrews has nothing to disclose.

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Name: Taylor D Andrews
Manuscript ID: JASN-2024-001321R1
Manuscript Title: Uremic Toxins, Chronic Kidney Disease, and Cognitive Dysfunction
Date of Completion: January 27, 2025
Disclosure Updated Date: January 21, 2025

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Employer: Mayo Clinic in Florida; Consultancy: Ionis Pharmaceuticals; Arialys Therapeutics; DynaMed (EBSCO); Ownership Interest: ANI Pharmaceuticals; and Research Funding: Amgen Pharmaceuticals; Eli Lilly.

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Name: Gregory S. Day
Manuscript ID: JASN-2024-001321R1
Manuscript Title: Uremic Toxins, Chronic Kidney Disease, and Cognitive Dysfunction
Date of Completion: January 22, 2025
Disclosure Updated Date: January 22, 2025

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Consultancy: ETTA Biotechnology; Resolution Therapeutics; and Research Funding: NIH: NIDDK/NIA, Regenerative Medicine Minnesota.

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Manuscript Title: Uremic Toxins, Chronic Kidney Disease, and Cognitive Dysfunction
Date of Completion: January 21, 2025
Disclosure Updated Date: January 21, 2025

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Consultancy: UCB, Janssen, Roche, Cerebral Therapeutics, Biohaven; Research Funding: UCB, Janssen, CSL Behring, and ONO Pharma; and Patents or Royalties: WO/2010/046716 entitled 'Neurological Autoimmune Disorders'.

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Name: Sarosh R Irani
Manuscript ID: JASN-2024-001321R1
Manuscript Title: Uremic Toxins, Chronic Kidney Disease, and Cognitive Dysfunction
Date of Completion: February 3, 2025
Disclosure Updated Date: February 3, 2025

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T. Kanekiyo reports the following:
Employer: Mayo Clinic Jacksonville; and Consultancy: Ono Pharma.

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Name: Takahisa Kanekiyo
Manuscript ID: JASN-2024-001321R1
Manuscript Title: Uremic Toxins, Chronic Kidney Disease, and Cognitive Dysfunction
Date of Completion: January 21, 2025
Disclosure Updated Date: January 17, 2025